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# Physiological and Nutritional Aspects of Obesity

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# Physiological and Nutritional Aspects of Obesity

By JEAN MAYER, Ph.D., D.Sc.*

There is little doubt that the prevalence of obesity in this country is on the increase (1) and that it is accompanied by increased mortality from a number of degenerative diseases (2) (Table 1). The relationship of disease and mortality is certainly more complex than the simple causation often suggested (e.g. 3). It is likely that, in many cases, the relationship between disease and obesity is association as well as causation: this is indicated by the fact that, while most correlations between causes of death and obesity are positive, there are at least two causes of death showing a negative correlation with obesity: suicide and tuberculosis (Table 1). (It has further been shown that the decrease in association of obesity and tuberculosis is not simply a matter of decreased intake following infection: long term studies show that there is a decreased probability of tuberculosis infection among "overweight" individuals (4) ). The degree of complexity which interrelationships between obesity and disease may reach is exemplified by the situation in middle age diabetes: this condition probably involves both associative factors (hyperphagia and diabetes being two facets of a common syndrome) and causative factors (the "lipoplethoric" state of adipose tissue contributes to the impairment of glucose tolerance, which can be improved by weight reduction (5) ). There is also the likelihood that the relationship between obesity *sensu stricto,* (i.e. excess *fat* accumulation) and disease has been obscured by the fact that the insurance tables which provide the bulk of available data were established, not in terms of individual fat content, but in terms of *weight.* Selected "overweight" groups, such as the California longshoremen studied by Breslow (6) have a favorable health picture. Body build *per se* shows correlation with certain diseases (7). In spite of these difficulties and complexities, it is still fair to say that the relationship of obesity and disease is close enough to allow obesity to be considered one of the most serious public health problems facing Western societies.

### *Definition and Determination of Obesity*

A definition of obesity has already been implied in the above paragraph. It is perhaps not useless however to emphasize that "obesity" is characterized by excessive fat accumulation (i.e. in excess of 20 per cent of the body weight in males, of 25 per cent in females). As such it is an entirely different concept from that of "overweight," which denotes a weight in excess of some norm for the height,

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# TABLE I

**Principal Causes of Death Among Men and Women Rated for Overweight. Attained Ages 25-74 Years**

**Ratio of Actual to Expected Deaths According to Estimates of Contemporaneous Mortality Experience on Standard Risks**

**Metropolitan Life Insurance Company, Ordinary Department, Issues of 1925 to 1934, Traced to Policy Anniversary, 1950**

| Cause of Death | Men | | Women | |
|---|---|---|---|---|
| | Deaths | % Actual of Expected Deaths | Deaths | % Actual of Expected Deaths |
| Principal Cardiovascular-Renal Diseases | 1,867 | 149 | 1,103 | 177 |
| Organic heart disease, diseases of the coronary arteries and Angina pectoris | 1,377 | 142 | 697 | 175 |
| Organic heart disease | 748 | * | 515 | * |
| Coronary disease and Angina pectoris | 629 | * | 182 | * |
| Cerebral hemorrhage | 247 | 159 | 226 | 162 |
| Chronic nephritis | 243 | 191 | 180 | 212 |
| Cancer, all forms | 385 | 97 | 476 | 100 |
| Stomach | 62 | 85 | 34 | 86 |
| Liver and gallbladder | 33 | 168 | 46 | 211 |
| Peritoneum, intestines and rectum | 103 | 115 | 93 | 104 |
| Pancreas | 19 | 93 | 21 | 149 |
| Respiratory organs | 39 | 78§ | — | — |
| Breast | — | — | 81 | 69 |
| Genital Organs | — | — | 132 | 107 |
| Uterus | — | — | 103 | 121 |
| Leukemia and Hodgkins Disease | 26 | 100 | 23 | 110 |
| Diabetes | 205 | 383 | 235 | 372 |
| Tuberculosis, all forms | 24 | 21 | 20 | 35 |
| Pneumonia, all forms | 98 | 102 | 78 | 129 |
| Cirrhosis of the Liver | 96 | 249 | 32 | 147 |
| Appendicitis | 76 | 223 | 41 | 195 |
| Hernia and intestinal obstruction | 39 | 154§ | 31 | 141§ |
| Biliary calculi and other gallbladder diseases | 32 | 152§ | 30 | 188§ |
| Biliary calculi | 19 | 206 | 50 | 284 |
| Ulcer of stomach and duodenum | 30 | 67 | — | — |
| Puerperal conditions | — | — | 43 | 162 |
| Suicide | 63 | 78 | 23 | 73 |
| Accidents, total | 177 | 111 | 74 | 135 |
| Auto | 76 | 131 | 27 | 120 |
| Falls | 32 | 131 | — | — |

*Satisfactory basis for comparison not available.

§Based on mortality rates on Standard risks for 1935-1939.

NOTE: Percentages which have been underlined indicate statistically significant deviations from experience on Standard risks.

usually that established on the basis of weights of insurance policy holders under 30. Extreme obesity is in general accompanied by overweight. There are numerous examples, however, both in experimental animals (8, 9) and in human subjects (10) where body fat can be increased to "obese" levels with enough atrophy of muscular tissues for "overweight" not to be present. Methods permitting diagnosis and determination of the extent of obesity have been excellently reviewed by Brozek and Keys (11). These methods include: visual observation, measurement of subcutaneous fat content with the aid of calipers and of soft tissue X-rays, determination of body density (with proper corrections for pulmonary buoyancy), and determination of total body water with resulting feasibility of calculation of total body fat.

### *Obesity as a Result of Hyperphagia*

Fat is quantitatively by far the most important form of energy storage. As a consequence, any situation, (other than growth, pregnancy and regeneration) where caloric intake is greater than caloric output will result in obesity. It has been demonstrated repeatedly that forced feeding of normal subjects, for example, will cause excessive fat accumulation in animals and man. However, equating obesity with the results of overeating, though frequently done by clinicians, health agencies and popular writers is no explanation: it merely redefines the problem by focusing attention on the mechanism of regulation of food intake and on its dysfunction which lead to intakes greater than expenditures (hyperphagia)*.

Furthermore, it is not correct to assume that because hyperphagia generally leads to obesity all obesities are necessarily due to *absolute* hyperphagia. It will be seen that in "metabolic" obesities (e.g., obesity due to ACTH-secreting tumors and the obese hyper-glycemic syndrome) strongly negative nitrogen balances accompany negative caloric balance so that an animal can be reduced to normal weight or even be made underweight and still retain its "obese" composition (i.e. a fat content several times the normal) (8, 9). Still, even in metabolic obesities, hyperphagia is usually present and certainly the relationship of obesity and hyperphagia is close enough to justify consideration of the mechanism of regulation of food intake in any study dealing with obesity.

### *Mechanism of Regulation of Food Intake: Localization of Structures, Multiplicity of Levels of Influence*

The earliest correlation reported between state of hunger and objective physiological phenomena was the finding by Cannon and Washburn (14) that sensations of hunger appeared simultaneously with contractions of the stomach.

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*The term "*relative*" hyperphagia is sometimes used to denote a situation where a positive caloric balance is arrived at as a result of normal intake and an output depressed to below normal (e.g. "immobilization obesity") in animals and men (12); "*absolute*" hyperphagia being a situation where food intake is elevated above the average *and* above expenditures; (the hyperphagia of diabetes or hyperthyroidism may just equate, or even fail to keep up, with expenditures; in one strain of mice studied by Fenton, a switch to high fat diets leads to increased intake and increased expenditure, the only authenticated illustration of "luxus consumption" (13) ).

The hunger contractions were further investigated by Carlson (15) who found that in starvation the frequency and intensity of the contractions of the empty stomach became progressively more pronounced in the course of the fast (at least until the fourth day.) Presence of such contractions is general in land vertebrates, whether homeotherms or poikilotherms. Carlson (15) followed by Quigley (16, 17) considered that an explanation of the hunger pangs is an explanation of "the control of hunger in health and disease." This theory received wide, if temporary, acceptance. However, Adolph (18) showed by diluting the ration of experimental animals with inert material that differences in "bulk" ("stomach filling property") of the diet had only a very transient influence; Grossman and Stein (19) found that vagotomy or sympathectomy which respectively eliminate the pattern of hunger contractions or the consciousness of them, while they eliminate the gastric component of hunger, do not affect the timing or the intensity of the extragastric components (feelings of weakness and emptiness associated with the desire for food).

Recent studies in human subjects (20, 21) and in experimental animals (22) have re-emphasized the excellent correlation between presence of hunger contractions and existence of a hunger state, hunger feelings and hunger behavior. Unpublished results (23) strongly suggest that damage to the ventromedial area of the hypothalamus impairs the response of gastric contractions to such agents as glucagon (vide infra). It thus appears that, while gastric contractions are not the basis of the regulatory mechanism, they are an important element in the consciousness of hunger, and that any theory purporting to represent regulation of food intake must account for the control of hunger gastric contractions.

### *Central Nervous System*

Pathological studies of patients with hypothalamic obesity first established the importance of this part of the central nervous system in the control of food intake (24). Experimental work by investigators on both sides of the Atlantic clearly eliminated pituitary lesions from the possible causes (25). The early development of our knowledge of this syndrome has been reviewed previously by Brobeck (26, 27) and by Mayer (28, 12). Identification of the regions in which discrete lesions will cause obesity was advanced by surgical exploration as well as by the use of stereotaxic instruments. The rat has been studied particularly by Hetherington and Ranson (29) (30) and by Brobeck and co-workers (26). They found that bilateral involvement of the ventromedial nuclei caused hyperphagia. Mayer and Barrnett (31) have since found that in the rat, unilateral destruction of the ventromedial nucleus causes slow development of obesity. Hypothalamic obesity in the mouse has been produced by Mayer et al (32), who found that in this species bilateral involvement of the ventromedial nuclei was necessary for the development of hyperphagia. In the monkey, Brooks (33) found that obesity follows superficial lesions of the base of the anterior hypothalamus. In the dog, Heinbecker (34) produced obesity by lesions caudal to the paraventricular nuclei. Development of the condition appeared to depend on the

interruption of descending fibres leaving the ventromedial nuclei. Conversely, Anand and Brobeck (35) found in rats that bilateral destruction of more lateral parts of the hypothalamus was followed by complete cessation of eating. Teitelbaum and Stellar (36) confirmed this finding although they found the inhibition was usually temporary. The areas destroyed included the extreme parts of the lateral hypothalamic nucleus at the same rostrocaudal level as the ventromedial nucleus. In a series of studies Morrison and Mayer (37, 38, 39) analyzed the mutual interrelationship of the adipsia and the aphagia produced by this type of lesion.

Stimulation of hypothalamic structures has proved equally informative. Brugger (40), who compiled the results of electrical stimulation in the hypothalamus reported by Hess (41), found that stimulation in the vicinity of the mamillothalamic tract produced morbid appetite not only for edible but also for indigestible material. Delgado and Anand (42) working on monkeys, found that temporary increases in food intake followed electrical stimulation of the lateral hypothalamus at the level of the ventromedial nucleus.

Larsson (43) made a particularly careful study of the results of electrical stimulation of the hypothalamus and the medulla and of intrahypothalamic injections in sheep and goats. He found that stimulation of the hypothalamus, just caudal to the optic chiasma backwards throughout the hypothalamus, lateral to the sagittal level through the columna fornix descendens and the mamillothalamic tract, resulted in hyperphagia. The most pronounced effect was obtained by stimulation of the region of the lateral hypothalamic nucleus, anterior to the columna fornix descendens or at the same transverse level as this tract. Rumination was seen on electrical stimulation of the same structures as give hyperphagia. Of particular interest was the fact that, as was previously observed by Magoun and by Hess, mastication, licking and swallowing could be elicited as single effects without the simultaneous occurrence of hyperphagia. Larsson felt that the concept implicitly or explicitly presented by Brugger (40) and by Anand and Brobeck (44) of the existence of a feeding center in the mamillothalamic area, or in the antero-lateral hypothalamus, was not strictly supported by his findings; although electrical stimulation of both these areas, particularly the latter, caused hyperphagia, the fact that extramasticatory and licking movements as well as hyperphagia were obtained diffusely in other areas support the conclusion that while the feeding pattern is closely related to regulation of food intake, the two mechanisms rest on centres which are in part differentiated. Similarly, it had been shown previously by Strom and Uvnas (45) that inhibition or activation of movements of the stomach and intestine could be caused by electrical stimulation of different hypothalamic areas.

Besides the hypothalamus, the thalamus appears to be involved in the regulation of food intake. Ruch and co-workers (46) showed that in the monkey damage to the ventromedial portion of the thalamus and rostral mesencephalic tegmentum caused obesity. The optic nuclei have been implicated by Rogers and Hardt (47) who showed that normal feeding habits were upset by destruction of

the optic nuclei. Separation of the frontal lobes from their thalamic connections also has been shown by Richter and Hawkes (48) to lead to obesity in rats. Similar findings obtained on lobotomized patients have been reviewed elsewhere (28). Finally, the importance of cortical phenomena in the regulation of food intake hardly needs to be emphasized. Kirschbaum (49) has shown that selective decortication may lead to hyperphagia.

Thus we are led to the concept that there are a number of structures concerned with the mechanism of regulation of food intake. Some are peripheral structures, in particular the stomach and possibly the intestine, the contractions of which, probably in part controlled by hypothalamic centers, are in turn one of the elements of consciousness of hunger, though perhaps not a quantitative determinant; oral structures play a limited role: it has been shown that rats will regulate their food intake even when the mouth is by-passed by feeding through gastric fistula (50). The most important regulating structures are a system of central areas, some situated in the hypothalamus, both centrally and laterally, some at intermediary points between the hypothalamus and the cortex and some cortical ones. Influences at these various levels, from a variety of stimuli, act on intake. It is of particular interest that recent behavioral techniques have permitted elucidation of the role of some of these structures, in particular the ventromedial nuclei.

### *Adjustment of Intake to Energy Output: Interrelationship of Metabolism, Hypothalamic Centers and Behavior*

Until a few years ago, studies of the regulation of food intake were hampered by lack of recording techniques: food intake was determined on a daily basis, or at best, for large animals and man, on a meal basis. New techniques permit the recording of every mouthful the animal takes (as well as every tongueful of water). Furthermore, new behavioral techniques have helped to clarify the physiological function of higher centers. Using a modification of the Skinner techniques of "operant conditioning" it has been found possible to follow and record for several days and even weeks the feeding behavior of animals, e.g. mice, with the ventromedial hypothalamic area damaged by stereotaxic lesions or by goldthioglucose (51). Under the conditions of the experiment, normal animals exhibited during the course of a day a period of rapid rate of eating followed by a period of satiety. Animals with ventromedial hypothalamic lesions do not show any increase of the rate of ingestion (which constitutes a behavioral measure of hunger) over the maximal rate of normal animals. But the "satiety" plateau has disappeared. This finding appears to confirm that the role of the ventromedial area is to brake a constantly activated feeding area. It was also shown that lesions of the ventromedial area due to goldthioglucose administration eliminate the increase in food intake, which in normal animals follows chronic exposure to cold and to exercise (52). It thus seems probable that the way in which the metabolic state intervenes to regulate food intake is through the modulation of inhibitory influences mediated through the ventro-

medial hypothalamic area. There are of course a number of other examples of somatic regulation where regulation is effected by modulating inhibitions, circulation for example.

The exact mode of interrelation of the hypothalamic centers is not yet altogether clear. In an important study Anand and Brobeck (44) showed that electrolytic lesions in the lateral hypothalamus caused aphagia. It has been shown since (37, 38, 39) that animals with such lesions also become completely adipsic. Daily loss of body weight in these animals is greater that that of rats subjected to pure starvation but the weight loss pattern is closely simulated by normal rats given access to food but completely deprived of water. Some rats showed spontaneous recovery of eating three to eight days post-operatively. The occurrence of such recoveries has also been noted by Teitelbaum and Stellar (36). In recovering animals, reappearance of water intake slightly preceded recovery of food intake. Recent work (23) has demonstrated that either hypodipsia or hyperdipsia may be present at the same time as hyperphagia, and that behavioral hyperdipsia (not due to diabetes insipidus) can be induced by hypothalamic lesions. Thus it appears that while there are of necessity interrelationships between regulation of water intake and regulation of food intake, the structures and mechanisms corresponding to these two functions can be dissociated.

The nature of the mediating mechanism between metabolic influences and hypothalamic inhibitory impulses is of obvious interest. A theory proposed by Strominger and Brobeck (53, 54) which saw heat phenomena, in particular those associated with specific dynamic action of food, *directly* regulating food intake, has been discussed at some length in an earlier review (12, 55). While it appears doubtful that such phenomena do in fact play a direct role in the quantitative adjustment of intake to requirements, a degree of facilitation or inhibition attributable to small temperature variations in the hypothalamus remains an interesting possibility. Souleirac suggested a limited but intriguing theory (56) which puts primary emphasis on carbohydrate absorption through the gastrointestinal tract. However, while it was confirmed that prolonged overconsumption of a high carbohydrate diet increases rates of intestinal absorption of glucose, this phenomenon has been shown to be secondary to the hyperphagia (57); while it may act to perpetuate dysfunctions, it is unlikely to have etiologic significance. It serves however as another reminder of the existence of a gastrointestinal component in the hunger-satiety complex.

The "glucostatic" hypothesis, proposed by the author and his associates (12, 55, 58, 59) and supported by Stunkard and his co-workers (20, 21, 60, 61) postulated that the influence of the metabolic state on feeding behavior and its role in regulating food intake were mediated through the rate of passage of glucose (or of ions associated with the passage of glucose, e.g., potassium and glucose phosphate) into the cells of the ventromedial hypothalamic area. The theory seemed difficult to test directly because of the apparent inaccessibility of this well-protected hypothalamic area. For this reason, efforts were concentrated at first on correlation of behavioral states with peripheral measurements of

glucose utilizations which could be considered generally representative of utilization by the critical midbrain area. In particular, it was shown (58) that in man, the presence or absence of hunger sensations in normal individuals subjected to various nutrition states, and in diabetic patients, correlated well with respectively small and large arteriovenous or capillary venous glucose differences ("Δ glucose"). These, of course, are indicators of availability of carbohydrates to extrahepatic tissues.

Stunkard and Wolff (20) confirmed these findings and in addition showed that the presence of gastric "hunger" contractions correlated well with subjective hunger feelings and small glucose values, while the absence of hunger contractions correlated well with absence of hunger feelings and large Δ-glucose values.

The fact that glucose infusions do not invariably eliminate hunger had been construed by Bernstein and Grossman (62) to be an insuperable objection to the glucostatic theory. The question was successfully re-examined by Stunkard and Wolff (20) who infused glucose in 40 normal and diabetic subjects. They administered 50 ml. of a 50 per cent solution. Gastric "hunger" contractions were eliminated in 19 subjects. Ten and twenty minutes after the infusion, arteriovenous differences were significantly higher in the subjects in whom gastric contractions were eliminated, indicating a more active utilization of carbohydrates. In 14 of the 19 subjects in whom the contractions had been stopped, contractions resumed, after a lapse lasting on the average 47 minutes. In the five other subjects A-V differences ("Δ-glucose") remained elevated.

A more reproducible method of increasing the availability of carbohydrates to non-hepatic tissues is through the administration of glucagon, the pancreatic glycogenolytic factor which apparently acts through activation of hepatic phosphorylase. Glucose thus released is well utilized and both blood glucose level and Δ-glucose are invariably increased when this hormone is administered. Over 50 experiments on human subjects have been conducted since the appearance of the first note on the effect of glucagon on gastric contractions (60). In all cases, gastric contractions and hunger sensations are immediately and strikingly eliminated by glucagon administration. At the same time, Δ-glucose values are drastically increased. As these, after a variable interval, wane, hunger sensations and gastric contractions reappear even at absolute levels of blood glucose which are still higher than the fasting values. Particularly striking is the observation of Stunkard (61) on a decorticate starved patient in whom continuous gastric hunger contractions were eliminated by glucagon administration while attempts by other methods (excluding food) had failed. The observations in human subjects on elimination of gastric contractions by glucagon have been reproduced in rats where the use of intragastric balloons has been introduced (22). In these animals it is possible to correlate the presence or absence of gastric contractions with behavior through the use of operant conditioning techniques (63).

An even more cogent indication in favor of a glucostatic component in the regulation of food intake is that goldthioglucose, but not other goldthio- compounds of similar toxicity, produces destructive lesions in the ventromedial

hypothalamic area (64, 65). These lesions are most severe in the ventromedial nuclei but also involve the ventral part of the lateral hypothalamic area, the arcuate nucleus and the median eminence. Goldthiosorbitol does not cause such lesions nor does it produce obesity, in spite of the structural similarity between glucose and sorbitol (65). Similarly, compounds in which gold is linked by a sulfur bridge to normal metabolites other than glucose, such as malic acid, caproic acid or glycerol, do not induce hypothalamic lesions or obesity. Goldthioglucose hypothalamic lesions can be induced in the rat as well as in the mouse (65, 66). It thus appears that gold is dragged into the ventromedial hypothalamic cells which it destroys because of the peculiar affinity for glucose displayed by these cells. This particular hypothalamic area had already been shown by Forssberg and Larsson (67) to exhibit an atypical glucose and phosphate metabolism. Incidentally, it is worthy of note that hypothalamic lesions induced by goldthioglucose are much more "purely" hyperphagic than lesions performed in the same area by electrocoagulation. Goldthioglucose obese animals do not display to the same degree the associated symptoms, such as gonadal dysfunction or disturbance in water balance, seen in animals made obese through hypothalamic lesions obtained by electrocoagulation (68). The histologic figures of goldthioglucose lesions also confirm that functional localization is not limited to a given nucleus but that greater or lesser densities of glucoreceptive cells with food intake regulating functions are to be found throughout the ventromedial hypothalamus, interspersed with cells performing other functions (65, 67). Thus we arrive at the following conception: there are a great many physiologic and psychologic factors influencing food intake; these may intervene at several levels in the central nervous system, in particular the lateral hypothalamic area, the thalamus, the frontal lobes and other parts of the brain cortex. Among these factors, the metabolic state of the organism is of particular importance; it is the factor which "regulates" food intake, i.e., which adjusts intake to output. At least part of the mode of action of this factor is through a glucostatic mechanism based on the ventromedial hypothalamus area. While a part of the awareness of hunger is through awareness of gastric contractions, (which in turn may be controlled in part by central deprivation) it appears that it is not through activation of hunger as such but through the application of a satiety brake that this ventromedial glucostatic mechanism operates.

The quantitative operation of the regulating mechanism is still mysterious. Some indication of the over-all characteristics are of course available. In the adult animals, Cowgill (69) and Gasnier and A. Mayer (70)* have shown that the intake is in constant ratio to the output. A. Mayer and his co-workers further showed that in caged animals the precision of regulation was better when the energy output was increased by exposure to cold. Recent studies (71, 72, 73, 74, 75) have shown that similarly, the precision of the regulation was better when animals and men have to perform moderate exercise than when they are inactive. In growing animals, food intake seems to be so determined that the thermochem-

*Summarized in 1955.

ical efficiency of growth, i.e., the ratio of calories deposited to calories ingested, is constant from weaning to puberty (76). On poorer diets, the thermochemical efficiency of growth declines somewhat earlier. It is also probable that besides the short term mechanism — probably glucostatic — operating to adjust intake to output, another mechanism, slower and somewhat sluggish, intervenes which corrects on a long-term basis imprecisions of the short-term mechanism and permits greater constancy of adult size and growth rate. It is possible that the operation of this slow long-term mechanism rests on the state of the fat depots at a given time (77, 55).

### *Multiple Etiology and Dual Pathogenesis of Obesity*

The development of the various forms of obesity can be considered from either the point of view of etiology or of pathogenesis. The point of view of etiology has been developed at length in a previous review (28) in which genetic, traumatic and environmental factors were distinguished (Fig. 1). Obviously, such a distinction, although useful, entails a certain degree of oversimplification; for obesity to develop, there has to be permissive interaction of genetic and of environmental factors, or of traumatic factors with genetic and environmental background. However, this very simplification permits a useful classification through singling out the characteristic element in the etiology. Table 2 is an adaptation of a table given in a more extensive review (12) which gives references for the different types cited.

The author and his associates (12) have also been led to introduce a general distinction between "regulatory" obesities, where the primary impairment is of the central mechanism regulating food intake, and "metabolic" obesities, where the primary lesion is an inborn or acquired error in the metabolism of tissues other than the regulating centers. In the first case, habitual hyperphagia may lead to secondary metabolic abnormalities. In the second case, peripheral metabolic dysfunction may in turn interfere with the proper function of the central nervous system. This difference has been illustrated in our laboratory by comparisons between different types of obesity in mice.

"Regulatory" obesities are illustrated by the hypothalamic obesities induced either by surgical (stereotaxic) bilateral destructions of the ventromedial nuclei (32) or by extensive symmetrical destructions in the ventromedial area after goldthioglucose administration (64). Mice with these syndromes show hyperphagia and their weights may reach four times the normal. Their rate of lipogenesis and cholesterogenesis (as measured by incorporation of radioacetate into hepatic and extrahepatic fatty acids and cholesterol, *in vivo* and *in vitro*) is increased in the measure that they are allowed to overeat. Fasting brings lipogenesis down to normal fasted levels. Their rate of glucose absorption by the intestine is increased, but this appears to be a secondary result of their "hyperphagia." When such obese animals are reduced by fasting, their body composition returns to normal as their weight returns to normal (12, 8, 9, 78). Animals made hyperphagic by conditioning also illustrate regulatory obesity (79).

## FIGURE 1

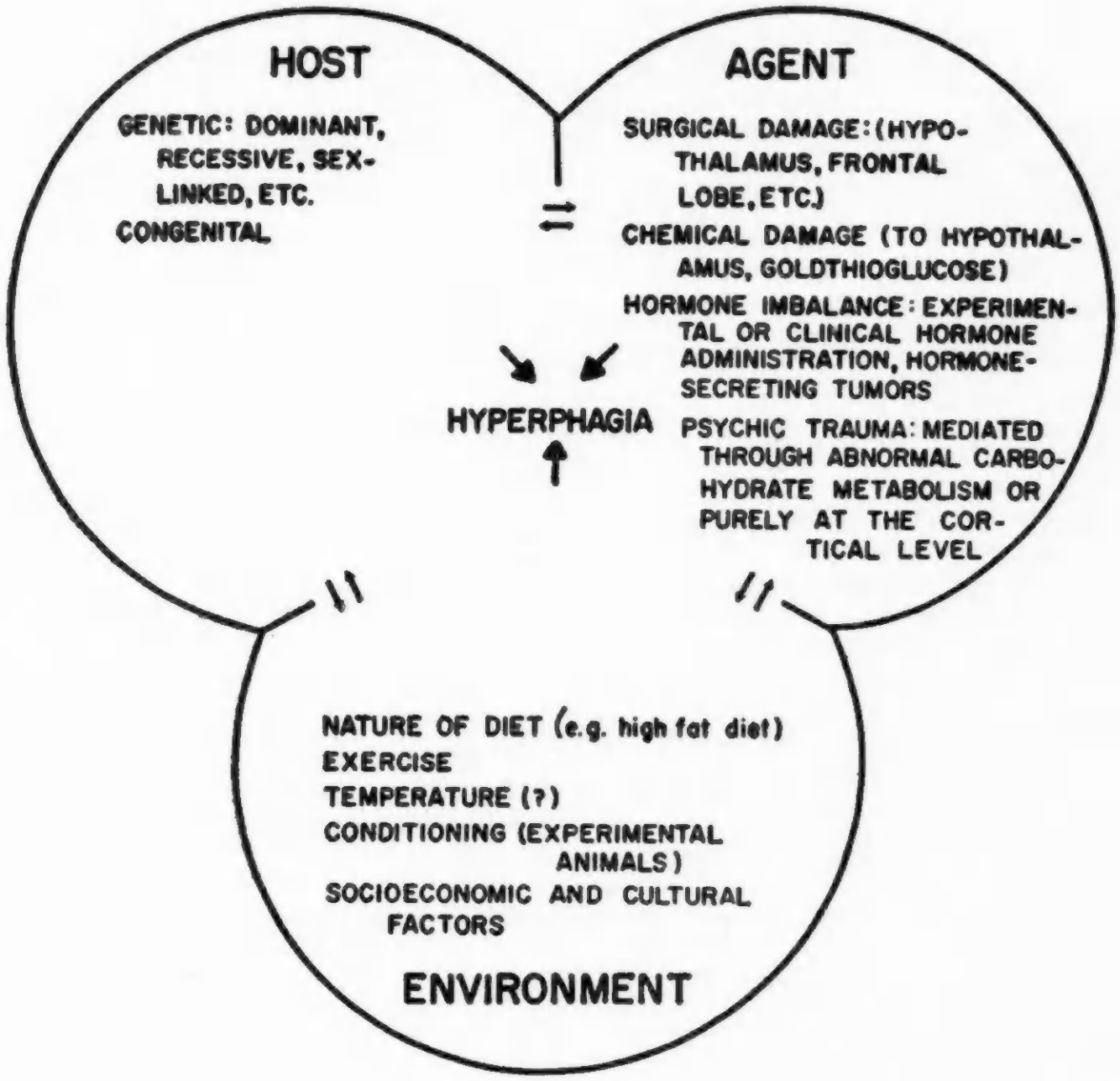
MULTIPLE FACTORS IN HYPERPHAGIA
HOST
GENETIC: DOMINANT, RECESSIVE, SEX-LINKED, ETC.
CONGENITAL
AGENT
SURGICAL DAMAGE: (HYPOTHALAMUS, FRONTAL LOBE, ETC.)
CHEMICAL DAMAGE (TO HYPOTHALAMUS, GOLDTHIOGLUCOSE)
HORMONE IMBALANCE: EXPERIMENTAL OR CLINICAL HORMONE ADMINISTRATION, HORMONE-SECRETING TUMORS
PSYCHIC TRAUMA: MEDIATED THROUGH ABNORMAL CARBOHYDRATE METABOLISM OR PURELY AT THE CORTICAL LEVEL
HYPERPHAGIA
NATURE OF DIET (e.g. high fat diet)
EXERCISE
TEMPERATURE (?)
CONDITIONING (EXPERIMENTAL ANIMALS)
SOCIOECONOMIC AND CULTURAL FACTORS
ENVIRONMENT

**Fig. 1. Causal factors in obesity classified according to the etiological concepts of host, agent and environment. For examples of obesities of these various origins in animals and man, see Table II. It must be emphasized that this scheme is an oversimplification: in fact genetic, traumatic, and environmental factors interact to cause relative or absolute hyperphagia.**

The situation in "metabolic" obesities such as the hereditary obese-hyperglycemic syndrome or the obesity due to the grafting of ACTH-secreting pituitary tumors is in striking contrast to that in regulatory obesities (Table 3).

Obese hyperglycemic mice (12) show an obesity as extreme as that seen in the hypothalamic types. Though their hyperphagia is usually less pronounced, they derive their caloric surplus in part from their relative inactivity. They are either markedly hyperglycemic or hyperglycemia can be readily elicited by administration of growth hormone, to which the blood glucose of normal littermates (or of littermates made obese by hypothalamic lesions — stereotaxic or gold-thio-glucose) shows little or no reaction. They show marked hypercholesterolemia. They display a variety of atypical responses to the effect of hormones. While means of "physical" defense against cold (such as piloerection, vasocontriction, etc.) are intact, obese hyperglycemic mice are incapable of raising their metabo-

## TABLE II — TYPES OF OBESITY

| | |
|---|---|
| **IN MICE** | |
| Genetic: | "Yellow" obesity, associated with coat color: heterozygous, dominant character; normal mating. "Hereditary obese hyperglycemic syndrome"; homozygous, recessive character associated with absence of mating. "NZO" obesity; homozygous recessive character, normal mating. |
| Of hypothalamic origin: | Spontaneous<br>Surgically induced<br>Induced by goldthioglucose. |
| Of endocrine origin: | Caused by injection of pituitary tumors secreting adrenocorticotrophic hormone. |
| Otherwise induced: | By high-fat diet. |
| **IN RATS** | |
| Genetic: | Associated with diabetes. |
| Of hypothalamic origin: | Induced by bilateral or unilateral lesions. |
| Of other central nervous system origin: | From frontal lobe damage. |
| Of endocrine origin: | From hypertrophy of adrenal cortical tissue.<br>From prolonged treatment with protamine zinc insulin, or insulin with forced feeding.<br>After thyroidectomy with hypothalamic lesions or with forced feeding. |
| Otherwise induced: | By immobilization.<br>By high-fat diet.<br>By conditioning. |
| **IN DOGS** | |
| Genetic: | In the Shetland sheepdog, recessive character. |
| Of hypothalamic origin: | Spontaneous.<br>Surgically induced.<br>Due to paraventricular degeneration caused by corticotrophin or cortisone. |
| Otherwise induced: | By immobilization. |
| **IN MONKEYS** | |
| Of hypothalamic origin: | Surgically induced. |
| Of other central nervous system origin: | Surgically induced by lesions of the thalamus. |
| **IN FARM ANIMALS** | |
| Genetic: | In strains selectively bred for fat, in particular, pigs bred for lard. |
| Of endocrine origin: | Induced by castration and by estrogens in the fowl; by castration and implants of estrogens in male cattle. |
| Otherwise induced: | By immobilization in pigs, cattle and geese; by forced feeding in geese for production of foie gras. |

| | |
|---|---|
| IN MAN | |
| Genetic: | A multiplicity of genes have been studied by Newman, von Vershuer, Bauer, Gurney, Rony, Angel and others.<br>In congenital adipose macrosomia.<br>In monstrous infantile obesity.<br>Associated with Laurence Moon Biedl syndrome.<br>Associated with hyperostosis frontalis interna.<br>Associated with von Gierke's disease.<br>in familial hypoglycemosis (congenital lack of alpha cells). |
| Of hypothalamic origin: | In dystrophia adiposogenitalis, with discrete or diffuse hypothalamic injury; occasionally with panhypopituitarism and narcolepsy; Kleine Levin syndrome. |
| Of other central nervous system origin: | After frontal lobotomy.<br>In association with cortical lesions, in particular, bilateral frontal lesions. |
| Of endocrine origin: | With insulin-producing adenoma of the islets of Langerhans, with diffuse hyperplasia of the islets, and in association with diabetes.<br>With chromophobe adenoma of the pituitary without hypothalamic inury.<br>In Cushing's syndrome (hyperglycocorticoidism).<br>From treatment with cortisone or adrenocorticotropic hormone.<br>In the Bongiovanni Eisenmenger syndrome.<br>In disorders of the reproductive system: gynandrism and gynism, aspermatogenic gynecomastia without aleydigism; male hypogonadism (sometimes with bulimia), postpuberal castration, menopause, ovarian disorder, paradoxical (Gilbert Dreyfus) disorder. |
| Otherwise induced: | By immobilization in adults and children.<br>By psychic disturbance.<br>By social and cultural pressure. |

## TABLE III

**Comparison Between Regulatory and Metabolic Obesities: Two Illustrations Which Have Been Obtained in Littermates: Goldthioglucose Obesity and Obese-Hyperglycemic Syndrome in Mice.**

| *Object of Comparison* | *Obese-Hyperglycemic Syndrome* | *Goldthioglucose Obesity* |
|---|---|---|
| Etiology | Mendelian recessive | 1 mg/g goldthioglucose |
| Pathology and Mechanism | Pancreatic dysfunction, hyperplasia of Islets of Langerhans, increased insulin and glucagon secretion. | Hypothalamic lesions: destruction of cells regulating intake in ventromedial area |
| Energy Balance | Positive through moderate hyperphagia, moderate or small increase in $O_2$ consumption, drastically decreased activity. | Positive through considerable hyperphagia |
| Effect of Nature of Diet | Maximum weight gain on high carbohydrate, less on protein, less or decreased on high fat. | Maximum weight gain on high fat diet, less on carbohydrate, decreased on high fat |
| Effect of Weight Reduction | Composition remains obese: i.e. animal loses nitrogen as well as fat, is still obese when weight normal or below normal. | Brings body composition back to normal |
| Resistance to Cold | Drastically reduced. | Normal |

## TABLE III (Continued)

| *Object of Comparison* | *Obese-Hyperglycemic Syndrome* | *Goldthioglucose Obesity* |
|---|---|---|
| Blood Glucose Levels | Generally hyperglycemic, further increased by growth hormone, etc. | Normal |
| Total Blood Lipids | Elevated | Elevated |
| Blood Cholesterol Levels | Elevated; further elevated by growth hormone, etc. | Normal |
| Effect of Hormones | Abnormal sensitivity to hyperglycemic effects of growth hormone, glucagon, etc. Increased resistance to insulin. | Normal |
| Mating behavior | Absent | Normal, though less frequent. Normal pregnancies and lactations. |
| Lipogenesis | Increased with hyperphagia, increased in fasting | Increased with hyperphagia, normal when fasted |
| Cholesterogenesis | Increased in fasting | Normal when fasted |
| Acetate pool and turnover | Increased pool; very much increased turnover. | Normal |
| Liver glycogen turnover | Very much increased | |
| Enzymatic activities | Increased liver phosphorylase | Normal phosphorylase |
| Intestinal Absorption | Increased in proportion to hyperphagia | Increased in proportion to hyperphagia |
| Body Composition, organ size | High body fat, decreased protein, cholesterol content increased with weight, enlarged liver, heart, pancreas, thymus, adrenals; decreased uteri, ovaries, brain. | High body fat, slightly increased protein; cholesterol content normal; enlarged liver, kidneys, ovaries and uteri |
| Retention of Steroid Hormones | Increased in proportion to body fat | Increased in proportion to body fat |
| Fed Ketone Levels | Slightly increased | Slightly increased |
| Effect of Fasting On Blood Ketones | Decreased | Normal elevation of blood ketones |

lism in the cold and as a result die rapidly when exposed to low temperatures. Mice with the obese-hyperglycemic syndrome show considerably hypertrophied islets of Langerhans, both as concerns alpha and beta cells, an increased pancreatic insulin (80) and glucagon content (81), which supports a previously postulated etiology (e.g. 82) of primary pancreatic dysfunction, namely increased insulin secretion and probably increased glucagon secretion. Such an etiology is supported by the fact that obese hyperglycemic mice show a sixfold increase in the rate of hepatic glycogen turnover (83) and in hepatic phosphorylase activity (84) (Glucagon is known to activate hepatic phosphorylase activity). Of particularly critical importance in the definition of "metabolic" obesity are the facts that in this syndrome, fasted rates of lipogenesis are increased over the fasted normal rates (85, 86), fasting does not cause hyperketonemia (87), and reducing the animals to normal weight by under feeding them does not bring body composition back to normal, but leaves them with a fat content still considerably increased over the normal at the expense of nonfat tissues (8, 9, 10, 78).

It is particularly interesting to note that another type of genetic obesity in mice, also associated with hyperglycemia, has been described recently by workers in New Zealand (88). These "NZO mice" exhibit a syndrome which, in spite of certain resemblances, is different from the hereditary obese-hyperglycemic syndrome. In particular, these animals mate and produce offspring (instead of having to be obtained by mating of non-obese carriers of the obese gene or by artificial insemination or ovum transplantation). Extensive metabolic studies have not yet been published by the discoverers of this syndrome but reaction of the blood glucose level to fasting appears quite different in these animals. The usually high blood sugar levels of NZO mice may go even higher during a fast instead of going down rapidly when food is withdrawn as in the hereditary obese hyperglycemic syndrome. In the NZO mice, low glucose values are observed during pregnancy, and very low values at parturition. Like the hereditarily obese hyperglycemic mice, the NZO mice show insulin resistance.

Mice made obese by grafting ACTH-secreting tumors show a number of metabolic abnormalities. Blood glucose levels are high in some animals. The blood sugars of all such mice show a remarkable stability under fasting conditions. Liver glycogen levels also remain higher than normal under fasting conditions, doubtless reflecting more active gluconeogenesis because of increase in circulating corticosteroids. Hepatic glucose-6-phosphatase activity is increased (while phosphorylase activity is normal, unlike the finding in the obese hyperglycemic syndrome (89). As in other forms of metabolic obesity (and characteristic of the class), the fasted rate of lipogenesis is greater than the normal fasted rate (90). When these animals are reduced to normal weight, their fat content is still much higher than normal (9) another feature typical of metabolic obesities. Another difference between regulatory and metabolic obesities is that animals with the metabolic obesities tested so far fail to show the normal rise in blood ketones which accompanies starvation (87).

Behavioral studies also emphasize the difference between regulatory and metabolic obesities in mice. Regulatory and metabolic types react differently to different diets. Similarly, the association with pathological conditions differs between the two classes (12). This has been analyzed, as regards the complex interrelationships between various types of obesity and diabetes, in a recent review on hyperglycemia (5).

### *Limitation of Normal Regulation Leading to Obesity*

Allusion has already been made to the fact that under conditions of reduced output, the regulation of food intake may become very imprecise (12, 71-75). A corollary is that when otherwise normal animals are placed under outlandish conditions the regulation of food intake may no longer adjust their intake to their energy output. Such a situation is encountered when animals are caged or their movements otherwise restricted (12, 34, 55, 71) or in man, when activity is decreased to extremely low levels (72, 73, 74, 75). It is also encountered in

certain strains of animals when these are fed a ration abnormally high in fat (13, 91, 92).

### *Extension of These Concepts to Man*

Some of the recognized etiologies of obesity in man are listed in Table 2. Literal extension to man of the examples worked out in the mouse or other experimental animals is not possible, though there are indications that certain non-ketotic types of diabetes associated with overweight in human subjects may be analogous to the hereditary obese hyperglycemic syndrome of mice. On the other hand, extension to man of the general concept of the existence of "regulatory" and "metabolic" hyperphagias (or anorexias) appears legitimate. For example, psychogenic obesities not mediated through metabolic disorders would be "regulatory;" endocrine obesities, "metabolic." Such a distinction between these two classes and the multiplicity of types within each class leads one to expect that obese patients may exhibit different reactions to the same treatment; in particular it may explain why certain patients find it easier to stay on certain reducing diets, others on diets of almost inverse composition. Some of the tests developed in experimental animals to distinguish between regulatory and metabolic obesities are being applied to groups of obese patients as a means of developing better diagnostic methods.

Finally, considerable evidence has been adduced that in man, too, the range of adaptation of normal regulation does not cover the complete range of possible energy expenditures; in adult man at very low activity ranges, appetite does not decrease in proportion to caloric output, with resultant accumulation of fat (72). In adolescents, obesity is more characteristically associated with inactivity than with intakes much in excess of normal (73). Conversely, vigorously exercising obese adolescents results in decrease of their fat content even when no attempt is made to control intake (74). These facts may be of particular importance in view of the prevalence of obesity in the school population (93).

## Practical Suggestions

The following suggestions may be found useful in the treatment of obesity:

### *General Attitude of the Therapist*

Obesity is not a moral issue. It is a complex medical problem. It cannot be cured by blaming the patient and shifting the entire responsibility for the treatment on him (or her).

### *Diagnosis of Obesity*

The mechanical application of "standard," "ideal" or "desirable" height-weight tables is not a proper diagnostic procedure. There are obvious weaknesses inherent in the construction of these tables. They are based on highly approximate heights ("with shoes on") and weights ("with ordinary clothing on")

of a biased sample (insurance policyholders at a time when such policies were much less widespread than they are now) of a population one or two generations ago. The reworking of the data rightly eliminated from calculations of averages those individuals over 30. It also introduced the concept of frames of various sizes but with no definition of such frames being given (94). In practice, extreme deviations from the average lead to immediate diagnosis of obesity (or emaciation) without any need for such tables. Smaller deviations cannot be interpreted without physical examination of the patient for skeletal size and muscular development. Since approximately half of the excess fat gets deposited directly under the skin, the old fashioned office or clinic technique of pinching (with or without calipers) is a cheap and simple substitute for underwater weighing, measurement of thiocyanate or deuterium space, etc.

### *Inducements to the Patient*

There is enough evidence to advocate weight reduction on the basis of health as well as esthetics but there are dangers in too much emphasis on threats of obesity to health as well as in excessive promises of reward if reducing succeeds (95). This is particularly important as regards children and adolescents (96).

### *Informing the Patient*

The importance of informing patients about their probable daily energy expenditure and about the caloric value of foods cannot be overemphasized.

Sound knowledge of the caloric value of foods will not only guide the patient during treatment, it will also protect him against the dishonest claims of manufacturers of "miracle foods" (such as "low-calorie" bread).

### *Use of Hereditary Data*

It has been shown repeatedly that obesity runs in families with genetic as well as environmental factors involved. Studies in the United States have shown that less than 10 per cent of the children of parents of normal weight are obese, but that the proportion rises to 40 to 50 per cent if one parent is obese and to 80 per cent if both parents are obese (28). Comparative lifetime studies of identical and fraternal twins have shown that food habits are *not* the main factor (28). Instead of denying the facts of heredity, it is more effective to use them (as was done with diabetes) to track down obese relatives and more important, to try to prevent the development of obesity in susceptible children. Obesity is most malignant when the onset is early.

### *Exercise*

The mechanism of regulation of food intake is apparently not adapted to function well at very low levels of activity. In many cases, adaptation to modern conditions without development of obesity implies that the person will have either to step up his activity or endure mild or acute hunger all his life. The

first alternative is difficult, especially in the United States and Canada, where the cities offer little inducement to walking and are often poorly provided with facilities for adult exercise. Even among the young, highly competitive team sports for the few are often emphasized at the expense of individual sports which all could learn and continue to enjoy after school and college years are over. If the first alternative, stepping up activity, is difficult, it is well to remember that the second alternative, lifetime hunger, is so much more difficult that to rely on it for weight control in cases of sedentary overweight can only continue to produce the fiascos of the past. Strenuous exercise on an irregular basis in untrained persons already obese is obviously not what is advocated here. But a reorganization of one's life to include regular exercise adapted to one's physical capacity is a sound preventive measure and a justified return to the wisdom of the ages. Moderate exercise during weight reduction, when practicable, also helps in promoting nitrogen balance and muscle tone.

### *Diets*

The essential principle to follow in devising the diets is that a good reducing diet is one on which the patient does not feel too hungry. The diversity of probable etiologies makes it likely that different patients will feel more comfortable on different types of diet. In practice, the choice of foods by obese individuals and their feeding patterns are as diverse as in normal subjects (97). It has been repeatedly found (97, 98, 99) that most obese patients tend to do their overeating late in the day and at night, which indicates that evening eating should be controlled with particular care. Diet prescription should be an individual operation, adapted to the patient's rate of energy expenditure and desired rate of weight loss. It should furnish an opportunity for education in the calorie value of foods. It should also permit nutrition education in general. Finally, it should be experimental; trial and error will permit the finding of the most effective diet, as well as the most suitable schedule of exercise. "Fad" diets may have a short term value but they have no lasting educational or practical worth. If, as some have claimed, it is possible to "shrink" the stomach, or "re-train the appetite," special diets might perhaps be used for that purpose before a change is made to a more normal diet. The evidence offered in favor of this process is, however, very scant. In some cases, better success is obtained with smaller and more frequent meals. The practice of eating slowly seems desirable on physiological grounds, since satiety mechanisms are likely to need time to take effect. It is desirable on psychological grounds also.

### *Obesity in Childhood and Pregnancy*

It seems undesirable as a rule to attempt to reduce weight in children or pregnant women. A better solution consists in keeping the child's weight at its existing value and letting the child "grow up" to the weight, and in letting *post partum* weight loss achieve at least part of the desired result in the woman. It is important to remember, when dealing with obesity in childhood, that inactivity

may be the major cause and that it may be easier and more effective to step up activity than to reduce food intake. Care must be exercised, particularly with children obese since early childhood, not to do more harm than good; with present methods, the prognosis for such subjects is generally poor and the psychological trauma of persistent and tactless attempts at reduction may be considerable (96).

### *Limitations of Potential Success*

Present day methods are often — if not generally — ineffective (100, 101, 102, 103). Some clinicians feel that attempts at weight reduction may even be undesirable for some patients on psychological grounds (95, 96). It has also been shown (104) that certain patients (who are probably those exemplifying "metabolic" obesities) are thrown into negative nitrogen balance on reducing diets even if these are of the high protein variety and that the weight of patients of this type returns rapidly to its original level when the period of treatment is over. Such findings emphasize the importance of typing obese patients from the point of view of general metabolism (e.g. carbohydrates, ketones) of hypothalamic functions, of anthropometric characteristics (somatotypes and distribution of excess fat) and of psychological idiosyncrasies.

Many other points of comparison would be (and have been) drawn. These presented here suffice to establish the fact the certain characteristics are nonspecific consequences of hyperphagia and obesity and found in both regulatory and metabolic obesities (e.g. increased fat content, increased intestinal absorption, increased total blood lipids, increased lipogenesis under ad libitum feeding); certain characteristics (e.g. increased lipogenesis and cholesterogenesis under fasting conditions, maintenance of a high fat content even when weight is reduced to normal or below normal levels, failure of blood ketones to rise normally when the animal is fasted) are general characteristics of metabolic obesities and are not found in regulatory obesities. Finally certain characteristics are specific for this or that metabolic obesity; for example, liver phosphorylase activity is elevated in the obese hyperglycemic syndrome; phosphorylase activity is normal, but hepatic glucose-6-phosphatase is increased in the obesity induced by ACTH-secreting tumors.

## CORRECTION

*Please make the following corrections in your March-April, 1958 copy of* Borden's Review, *"Amino Acid Supplementation," by Dr. E. E. Howe. We apologize for printing the errors. — The Editors.*

Page 25, paragraph 2, line 12: "It however contained only 27% glutamic acid whereas 89% of the other mixtures was made up of this amino acid. As the author is well aware, it is doubtful that a mixture containing 89% of any amino acid can be well balanced biologically."

Page 30, line 1: 0.5% should be 0.05%.

Page 34: Reference 75 should be *J. Nutrition* instead of ibid.

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